

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Sibley et al.)	Group Art Unit unknown
)	
Appl. No.	:	unknown)	
)	
Filed	:	herewith)	
)	
For	:	ST-B17 SEROTONIN RECEPTOR)	
)	
Examiner	:	unknown)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to examination on the merits, please amend the application as follows:

IN THE SPECIFICATION:

On page 1, after line 1, please insert:

Related Applications

This application is a continuation of U.S. Pat. Appl. No. 08/428,242, filed September 18, 1995, which claims the benefit of priority of International Appl. No. PCT/US93/10296, filed October 26, 1993, which claims the benefit of priority of U.S. Appl. No. 07/970,338, filed October 26, 1992.

Appl. No. : unknown
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REMARKS

Applicants wish to thank Examiner Allen for the courtesy extended to their representative, Nancy W. Vensko, on January 22, 2001, in U.S. Pat. Appl. No. 08/428,242, filed Sept 18, 1995. The Interview Summary Form PTOL-413 summarizes the discussions held at the personal interview (attached). The present remarks address the substance of the Examiner Interview.

I. Disposition Of Claims

Claims 1-16 are presented for examination.

II. Human and Rat Serotonin Receptor Protein St-B17

The invention relates to isolated human serotonin receptor protein St-B17 (Claim 1) and isolated rat serotonin receptor protein St-B17 (Claim 9), and related constructs, polynucleotides, cell lines, and products-by-process.

III. No New Sequence Listing

While disagreeing with the position by the PTO that depositing a biological material after the priority date introduces new matter into this application, to advance prosecution Applicant has refrained from introducing a biological deposit or deposit information herein. Neither has Applicant introduced a new sequence listing in paper form or computer readable form (CRF) into this application to conform to any biological deposit. Rather, Applicant has copied the *original* sequence listing in paper form and computer readable form (CRF) that was filed in response to the Notice to Comply in the parent application to which this continuation application relates back.

IV. Corrected Rat and Human Sequences

Under 37 CFR 1.56, Applicant wishes to meet his duty to disclose by making of record errors in the sequence listing.

Beginning with rat, SEQ ID NO:7 is the DNA sequence and SEQ ID NO:8 is the amino acid sequence encoding rat serotonin receptor protein St-B17, as originally filed on October 26, 1992. The inventors and their colleagues subsequently published this

Appl. No. : **unknown**
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sequence as Monsma et al., Molecular Pharmacology 43:320 (March 1993) (attached). Other colleagues published this sequence as Ruat et al., Biochem Biophys Res Comm 193:268 (May 1993) (attached). Later, the inventors and their colleagues published the corrected sequence in Kohen et al., J. of Neurochemistry 66:47 (1996) (attached), which points out the particular changes in both the DNA and amino acid sequences.

Turning to human, SEQ ID NO:12 is the DNA sequence and SEQ ID NO:13 is the amino acid sequence encoding human serotonin receptor protein St-B17, as originally filed on October 26, 1993. The inventors and colleagues subsequently published the corrected sequence in Kohen et al., supra. Exhibit 1 (attached) points out the particular changes in the DNA sequence, and Exhibit 2 (attached) points out the particular changes in the amino acid sequence.

V. Claiming by Crucial Third and Sixth Transmembrane Domains

The claims are directed to isolated human serotonin receptor protein St-B17 (Claim 1) and isolated rat serotonin receptor protein St-B17 (Claim 9), and related constructs, polynucleotides, cell lines, and products-by-process, where the serotonin receptor protein St-B17 is defined by reference to crucial transmembrane domains III and VI. Trends in Pharmacology 13:160 (April 1992) (attached) shows that, at the time of the Oct 26, 1992 priority date of the present application, most serotonin receptors were known to be G protein-linked receptors having a putative seven transmembrane domain structure. Here is Trends in Pharmacology Figure 3 showing putative transmembrane domains numbered I to VII for previously known serotonin receptors:

TODAY'S PREDICTION

	I	II	III	IV	V	VI	VII
5-HT _{1Bβ} (mouse)	(48) -VALLALITLATTLSNAFVIATVYRTRKLHTPANYLIASLAVTDLLVSILVMPISTMYTVT						
5-HT _{1Dα} (dog)	(41) -ALLLSIITMATALSNAFVLTTIFLTRLKLIHTPANYLIGSLAMTDLLVSILVMPISIAYTTT						
5-HT _{1Dα} (human)	(41) -AVVLSVITLATVLSNAFVLTTILLTRKLHTPANYLIGSLATTDLVSVLVPMAALYQVL						
5-HT _{1A} (rat)	(39) -SLLLGTGLIFCAVLGNACVVAIALERSILQNVANVLIGSLAVTDLMSVLVLPMAALYQVL						
5-HT _{dro2A}	(229) -SVLLGMLILVTIIGNVFVIAAIILERNILQNVANVLVASLAVADLFVACLVMPLGAVYEIS						
5-HT _{dro2B}	(80) -AVVLGMLILVTIIGNVFVIAAIILERNILQNVANVLVASLAVADLFVACLVMPLGAVYEIS						
5-HT _{dro1}	(165) -SIVLLIVILGTVVGNVLVCIAVCVMRKLRPCNYLLVSLALSALCVALLVMPMALLYEV						
5-HT _{1C} (rat)	(57) -ALSIVVIIIMTIGGNILVIMAVSMEKKLNATNYFLMSLAIADMILVGLVMPLSLLAILY						
5-HT ₂ (rat)	(77) -ALLTTVVIILTIAGNILVIMAVSLEKKLNATNYFLMSLAIADMILVGLVMPVSMLTILY						
5-HT _{1Bβ} (mouse)	G-RWTLGQVVCFWLSSDITCCTASIMHLCVIALDRYWAITDAVEYSAKRTPKRAAIMIV						
5-HT _{1Dα} (dog)	R-TWSFGQILCDIWLSDDITCCTASILHLCVIALDRYWAITDALEYSKRRTAGRAAVMIA						
5-HT _{1Dα} (human)	H-TWNFGQILCDIWLSDDITCCTASILHLCVIALDRYWAITDALEYSKRRTAGHAATMIA						
5-HT _{1A} (rat)	N-KWTLGQVTCDFLIALDVLCCTSSILHLCAIALDRYWAITDPIDYVNKRTP-RPRALIS						
5-HT _{dro2A}	Q-GWILGPELCDIWTSCDVLCCASILHLVAIAVDRYWAVTN-IDYIHSRTSNRVFMMIF						
5-HT _{dro2B}	N-GWILGPELCDIWTSCDVLCCASILHLVAIAADRWTVTN-IDYNNLRTPRRVFLMIF						
5-HT _{dro1}	E-KWNFGPLLCDIWVSDFDVLCCASILNLCAISVDRYLAITKPLEGVKRTPRRMMLCVG						
5-HT _{1C} (rat)	DYVWPLPRYLCPPWISLDVLFSTASIMHLCASISSLDRYVAIRNPIEHSRFNSRTKAIMKIA						
5-HT ₂ (rat)	GYRWPLPSKLCAIWIYLDVLFSTASIMHLCASISSLDRYVAIQNPPIHHSRFNSRTKAFLKII						
5-HT _{1Bβ} (mouse)	LWVVFISISISLP-PFF-WRQAK--AEEEMLDCFVNNTDHVLYTVYSTVGAFYLPTLLLIAL						
5-HT _{1Dα} (dog)	TVWVISICISIP-PLF-WRQAK--AQEDMSDCQVNTSQISYTIYSTCGAFYIPSVLLIIL						
5-HT _{1Dα} (human)	IVWAISICISIP-PLF-WRQAK--AQEEMSDCLVNNTSQISYTIYSTCGAFYIPSVLLIIL						
5-HT _{1A} (rat)	LTWLIGFLISIP-PILGWRTP--DRSDPACTISKDH-GYTIYSTFGAFYIPLLLMLVL						
5-HT _{dro2A}	CVWTAAVIVSLA-PQFGWKDPDYLQRIEQQKCMVS-QDVSYQVFATCCTFYVPLMVILAL						
5-HT _{dro2B}	CVWFALIVSLA-PQFGWKDPDYMKRREEQHCMVS-QDVGYQIFATCCTFYVPLLVILFL						
5-HT _{dro1}	IVWLAAACISLP-PLLIL-GNEHEDEEGQPICTVC-QNFAYQIYATLGSFYIPLSVMLFV						
5-HT _{1C} (rat)	IVWAISIGVSVPIPVLIGRLDESKVFNNTT-CVLNDPN--FVLIGSFVAFFIPLTIMVIT						
5-HT ₂ (rat)	AVWTISVGISMPIPVFGQLQDDSKVF-KEGS-CLLADDN--FVLIGSFVAFFIPLTIMVIT						
5-HT _{1Bβ} (mouse)	YG-RIYVEARSRLIKQ - (57) - EKKKLMARERKATKTLGIILGAFIVCWLPFFII						
5-HT _{1Dα} (dog)	YG-RIYVAARNRILNP - (55) - ERKRISAARERKATKTLGIILGAFIVCWLPFFVAS						
5-HT _{1Dα} (human)	YG-RIYRAARNRILNP - (55) - ERKRISAARERKATKILGIILGAFIVCWLPFFVVS						
5-HT _{1A} (rat)	YG-RIFRAARFRIRKT - (101) - AKRKMLARERKTVKTLGIIMGTIFLCWLPFFIVA						
5-HT _{dro2A}	YW-KIYQTARKRIHRR - (316) - RKTETLEAKRERKAAKTLAIITGAFVVCWLPFFVMA						
5-HT _{dro2B}	YW-KIYIIARKRIQRR - (235) - RRQLLEAKRERKAAQTLAIITGAFVICWLPFFVMA						
5-HT _{dro1}	YY-QIFRAARRIVLEE - (83) - KKLRFQLAKEKKASTTLGIIMSAFTVCWLPFFILA						
5-HT _{1C} (rat)	YFLTIYVLRRQTLMLP - (50) - RGTMQAINNEKKASKVLGIVFFVFLIMWCFFITN						
5-HT ₂ (rat)	YFLTIKSLQKEATLCG - (41) - RKTMKSIISMEQKACKVLGIVFFLFVVMWCFFITN						
5-HT _{1Bβ} (mouse)	LVMPICKDACW--FHMAIFDFFNWLGYLNSLINPIIYTMFNEDFKQAFHKLIRFKCAG						
5-HT _{1Dα} (dog)	LVLPICRASCW--LHPALFDFTTWLGYLNSLINPIIYTVFNEEFRQAFQKIVPFRKAS						
5-HT _{1Dα} (human)	LVLPICRDSCW--IHPALFDFTTWLGYLNSLINPIIYTVFNEEFRQAFQKIVPFRKAS						
5-HT _{1A} (rat)	LVLPFCESSCH--MPTLLGAIINWLGYNSLNNPVIYAYFNKDFQNAFKKIICKCFCCR						
5-HT _{dro2A}	LTMPLCAA-CQ--ISDSVASLFLWLGYFNSTLNPIYTFISPEFRQAFKRILFGGHRP - (8)						
5-HT _{dro2B}	LTMSLCKE-CE--IHTAVASLFLWLGYFNSTLNPIYTFISPEFRRAFKRILFGGRKAA - (8)						
5-HT _{dro1}	LIRPF--ETMH--VPASLSSLFLWLGYANSLLNPVIYATLNDRFRKPFQEILYFRCSS - (36)						
5-HT _{1C} (rat)	ILSVLCGKACNQKLMEKLLNVFVWIGYVCSGINPLVYTLFNKIYRRAFSKYLRCDYKP - (69)						
5-HT ₂ (rat)	IMAVICKESCNENVIGALLNVFVWYGYLSSAVNPLVYTLFNKYRSAFSRYIQCQYKE - (70)						

Fig. 3. Aligned amino acid sequence homologies of 5-HT receptors. Tint shows positions where more than 6 out of the 9 sequences are identical. Putative transmembrane domains are numbered I to VII. Numbers in parentheses correspond to amino acids not represented. Arrow after domain VII indicates amino acid whose charge varies depending on how the receptor is coupled with second messenger systems. Data from Refs 6, 9–11, 19, 20.

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The patent specification (at Example 1, page 8, line 30 et seq.) shows that, beginning with sequences that were derived from the third and sixth transmembrane domains of previously known G protein-linked receptors, the present inventors cloned and expressed a rat cDNA that encoded a novel serotonin receptor called St-B17 with high affinity for tricyclic psychotropic drugs. The pat spec (at page 12, line 15 et seq.) additionally shows that hydropathy analysis of the deduced amino acid sequence indicated seven hydrophobic regions predicted to represent putative transmembrane domains I-VII. The pat spec (at page 12, line 22 et seq.) further shows that when compared with previously known G protein-coupled receptors, the transmembrane domains of St-B17 exhibited homologies of 41%, 40%, 39%, 38%, 37%, and 36% to 5-HT2, 5-HT1D, 5-HT1C, 5-HT1B, 5-HT1A, and 5-HT1E serotonin receptors, respectively.

As indicated in Kohen et al., *supra*, a frame shift error had occurred in the rat clone, but the error occurred in the long carboxyl terminus tail, well past the seven transmembrane domains. As shown in Exhibits 1 and 2, a frame shift error had occurred in the human clone, too, but the error occurred in the long carboxyl terminus tail, well past the seven transmembrane domains, also. Monsma et al., *supra*, Figure 1, and Ruat et al., *supra*, Figure 1 for rat, and Kohen et al., *supra*, Figures 1 and 2 for human, illustrate the seven transmembrane domains. Trends in Pharmacology, *supra*, shows that, at the time of the Oct 26, 1992 priority date of the present application, transmembrane domain III and VI were known to contain conserved amino acids that were presumed to interact with the ligand, serotonin. Consistent with this information and the pat spec (at page 8, lines 31-34), the invention is claimed by reference to crucial transmembrane domains III and VI, the sequence from which was derived the degenerate primers to clone the rat cDNA encoding the novel serotonin receptor called St-B17.

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VI. Monsma et al., Ruat et al., and Kohen et al.

As indicated above, the inventors cloned and expressed a novel serotonin receptor. There is no identity with other serotonin receptors as shown by the fact that the transmembrane domains of St-B17 exhibited homologies of 41%, 40%, 39%, 38%, 37%, and 36% to 5-HT2, 5-HT1D, 5-HT1C, 5-HT1B, 5-HT1A, and 5-HT1E serotonin receptors, respectively (see *supra*). Additionally, the above dates show that Monsma et al. and Ruat et al., describing the cloning of the rat St-B17 serotonin receptor, occurred at a time *after* the Oct 26, 1992 priority date of the present application in which the cloning of the rat St-B17 serotonin receptor is disclosed. Furthermore, the above dates show that Kohen et al., describing the cloning of the human St-B17 serotonin receptor, occurred at a time *after* the Oct 26, 1993 priority date of the present application in which the cloning of the human St-B17 serotonin receptor is disclosed. Because these scientific publications are not *prior art*, they cannot bar patentability of the present invention.

Conclusion

In view of the foregoing, Applicant respectfully requests that the present amendment be entered prior to examination of this application. It is respectfully submitted that the present application is in condition for allowance. Should any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/10/01

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